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TITLE: Do Capacity Coupled Electric Fields Accelerate Tibial Stress Fracture Healing

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14. ABSTRACT Purpose: To determine the effect of capacitively coupled electric field stimulation on tibial stress fracture healing in men and women. Methods: A convenience sample of 20 men and 24 women with posteromedial tibial stress fractures was recruited. Subjects were randomly assigned an active or placebo OrthoPak® Bone Growth Stimulator (sinusoidal wave, 3-6 V, 60 kHz, 5-10 mA), to be used for 15 hours per day until healed. Subjects were given supplemental calcium and instructed to rest from training. Healing was confirmed when hopping 10 cm off the ground for 30 seconds was pain free. Data was analyzed using 2-way ANOVA for effects of treatment and sex on healing time. Compliance and other between-group differences and relationships were examined via ANOVA, t-tests and correlation analyses. The influence of anthropometric and behavioral characteristics on time to healing was evaluated by multiple regression analysis. Results: No difference in time to healing was detected between treatment and placebo groups. Treatment compliance was positively associated with reduced time to healing (p = 0.003). Rest non-compliance was associated with increased time to healing (p = 0.05). Female subjects healed more slowly than men (p = 0.05). Conclusions: Capacitively coupled electric fields did not accelerate tibial stress fracture healing in comparison with placebo treatment (modified rest), but women took longer to recover than men. Daily device use and weight bearing loading during treatment appeared to positively and negatively (respectively) influence the efficacy of the active device.				
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INTRODUCTION:

Subject and Purpose: A double blind randomised controlled study was designed to determine if capacitively coupled electric field stimulation could accelerate the healing of the most commonly occurring tibial stress fractures. Additionally the ability of tibial stress fractures to be graded for severity on four different diagnostic imaging modalities (plain films, nuclear medicine scans, MRI and CT) was examined. The purpose of the imaging study was to determine the most cost effective approach for tibial stress fracture radiological diagnosis and to identify the imaging modality that most effectively predicts time to healing, with and without electric field stimulation. A convenience sample of men and women was recruited in order to discriminate gender effects. All subjects were treated in an identical fashion with an active or inactive electric field stimulator device (active devices applied a sinusoidal wave of 3-6 V, 60 KHz, 5-10 mA.) Subjects wore the units for 15-20 hrs/day until healed (pain free for 30 seconds of hopping on the affected limb). **Scope:** While our findings are most directly applicable to community dwelling, tibial stress fractured athletes engaged in activities involving repetitive loading of the lower extremity, it is likely that the results of the trial can be applied to individuals similarly loading their skeletons in other settings (such as the military), as well as other long bones effected by stress fracture at primarily cortical sites.

BODY:

Research accomplishments with respect to the Statement of Work, are described in the context of an unorthodox award period. The original Statement of Work described a three-year study to be completed at Stanford University from September 1998 to September 2001. In actuality, a move to Australia in 1999 by the study coordinator precipitated a subcontract from Stanford to Griffith University to complete the trial. The administrative process associated with this novel initiative was very prolonged. Indeed, it was March 15, 2003 when the final approval letter from the US Army HSRRB was received by the Griffith investigators indicating data collection could recommence. Data collection proceeded very smoothly from that time. A number of no-cost extensions were necessary to re-establish a realistic data collection and reporting period.

Research accomplishments associated with tasks outlined in the approved Statement of Work.

The original Statement of Work indicated: "A convenience sample based on flow of tibial stress fracture cases at local Sports Medicine Clinics will be selected, thus no exact Statement of Work can be provided. It is, however, planned that the process of subject recruiting, evaluation, treatment and follow-up will occur over period of two to three years beginning as soon as funding becomes available and ending when forty subjects have been treated. It is predicted that some periods of the year will produce more subjects than others, according to the seasonal nature of athletic events associated with high incidence of tibial stress fracture." Indeed, the flow of subjects occurred much as was predicted by this Statement. Fifteen subjects were recruited in the eighteen months the study ran at Stanford University, of whom two subjects were excluded from the final analysis. A further 35 data sets were collected during the three years of recruiting at Griffith University, of which four were excluded from the final analysis.

Tasks outlined in the following original (1998) timeline were fully achieved, albeit in a modified timeframe attributable to the constraints described above.

Original Timeline:

Year 1	Year 2	Year 3
1. Interact with Sports Medicine Clinicians and Radiologists to establish standards of evaluation. 2. Purchase supplies. 3. Recruit and treat ~ 16 subjects, analyze images.	4. Recruit and treat ~ 16 subjects, analyze images. 5. Prepare interim report. 6. ACSM meeting, present preliminary data	7. Recruit and treat final (8) subjects, analyze images. 8. Prepare final report. 9. ACSM meeting, present findings

Original Statement of Work activities:

<u>Preliminary Activities:</u>	<u>Level of accomplishment:</u>
Meetings and discussion with Sports Medicine Clinic physicians	Completed
Purchasing supplies	Completed
<u>Ongoing Activities:</u>	
Referral of subjects and discussion with referring clinicians	Completed
Subject consultation with Study Physician and data recording (injury evaluation, subject data, Food Frequency and Activity Questionnaires, OrthoPak training)	Completed
Imaging appointment making and subject confirmation	Completed
Radiologist consultation and severity grading of images	Completed
Subject monitoring	Completed
Weekly phone calls	
Weekly office visits	
Follow-up subject consultation with Study Physician when asymptomatic	Completed
Appointment making for follow-up imaging	Completed
Radiologist reliability test	Completed
Statistical analysis	Primary outcomes analysed for reporting
Report writing	Secondary manuscript in preparation

Revised Statement of Work provided in conjunction with an October, 2003-Sept 2005 request for no-cost extension:

<u>Activities still to be completed:</u>	<u>Level of accomplishment:</u>
<i>Oct 2003-Sept 2004</i>	
1. Recruit and treat 10 subjects	1. 14 data sets recruited and treated
<i>Oct 2004-Sept 2005</i>	
2. Recruit and treat remaining 4 subjects	2. Additional 3 data sets recruited and treated
3. Complete comparison study of radiological images from each patient and radiologist reliability test (To be completed at Stanford University, School of Medicine by Study Radiologist Bergman and colleagues, with assistance from Beck, Study Coordinator)	3. 4 x grading of entire radiology data set completed (1. CA, USA, May 2005; 2. QLD, Aust, Sep 2005; 3 & 4. MN, USA, Sep 2006)
4. Analyse data	4. Primary outcome data analysed, preliminary analysis of radiology data
5. Prepare final report	5. NA (see below)
6. Present study findings at annual meeting of the American College of Sports Medicine	6. NA (see below)
7. Prepare publication	7. Manuscript prepared, abstract submitted for 2006 ACSM
<u>Ongoing Activities:</u>	
1. Recruitment of subjects and liaison with referring clinicians	All ongoing activities completed
2. Subject consultation and data recording (injury evaluation, Lifestyle, Food Frequency and Activity Questionnaires, OrthoPak® training)	
3. Imaging appointment making and accompanying	
4. Subject monitoring	
a. Phone calls or emails every 2 days	
b. Weekly office visits	
5. Follow-up consultation when asymptomatic	
6. Appointment making for follow-up MRI	
7. Bone density evaluation	
8. Follow-up thank-you letters and subject progress reports to referring clinicians	

In August 2005, although data collection had been completed, a final request for a no-cost extension was submitted on the following basis:

“Per the original grant agreement, it is planned to present study outcomes at the annual scientific meeting of the American College of Sports Medicine. As it was only possible to unblind our study devices in March of this year (2005) we were unable to submit an abstract to the 2005 ACSM meeting. Instead, we plan to submit by the deadline this year (November 2005) for the upcoming ACSM to be held in Denver, Colorado, May 31 - June 3, 2006.”

September – December 2005	<u>Level of accomplishment:</u>
1. Complete second radiology reading of all 200 imaging series (scheduled)	1. Completed Sep 2005
2. Complete 6-month follow-up re-injury survey of subjects (underway)	2. Completed
3. Continue control subject bone density measures (underway)	3. Completed
4. Continue data analysis and interpretation (underway)	4. Primary outcome data analysis completed
5. Prepare ACSM abstract based on primary study objectives and submit (November, 2005)	5. ACSM abstract submitted and presented Denver 2006
6. Begin writing papers <ul style="list-style-type: none"> a. Primary outcome data (OrthoPak treatment effect) b. Secondary study outcome data (radiological analysis) 	6. Papers: <ul style="list-style-type: none"> a. Treatment effect paper completed (Appendix 1) b. Radiology paper in progress (abstract submitted 2007 ACSM – see Appendix 2)
7. Write annual ethics reports to: <ul style="list-style-type: none"> • US Army Human Subjects Research Review Board • Stanford University panel on Human Subjects in Medical Research • Australian Defense Human Research Ethics Committee • Griffith University Human Research Ethics Committee 	7. Annual reports submitted to <ul style="list-style-type: none"> • US Army Human Subjects Research Review Board • Stanford University panel on Human Subjects in Medical Research 8. Final reports submitted to <ul style="list-style-type: none"> • Australian Defense Human Research Ethics Committee • Griffith University Human Research Ethics Committee

December 2005 – August 2006	<u>Level of accomplishment:</u>
1. Complete control bone density measures	1. Completed
2. Complete all data analyses	2. Primary outcome analyses completed. Secondary outcome measures largely analysed.
3. Prepare and present primary outcomes at ACSM, Denver, CO (May/June 2006)	3. Completed
4. Complete papers	4. Primary paper completed, secondary paper initiated
5. Submit papers to journals	5. Primary paper submitted
6. Write final report to U.S. Army Medical Research and Materiel Command	6. Final report in preparation (current document)
7. Submit final ethics reports to: <ul style="list-style-type: none"> US Army Human Subjects Research Review Board Stanford University panel on Human Subjects in Medical Research Australian Defense Human Research Ethics Committee Griffith University Human Research Ethics Committee 	7. Final ethics reports: <ul style="list-style-type: none"> Current document? In preparation Completed Completed

Data presentation.

To achieve adequate statistical power for analysis of treatment and gender effects, we determined a minimum of 40 subjects (20 men and 20 women) were required in the study sample. Ultimately, data collection was initiated on a total of 50 subjects (21 male, 29 female) of which 44 were completed satisfactorily. The final data set to evaluate treatment effects included 20 men and 24 women. Of subjects in the final data set, nine men and fourteen women were allocated active devices. Eleven men and ten women were allocated placebo devices.

The single male data set to be excluded was considered, on reflection, to suffer a tibial stress fracture sufficiently atypical as not to conform to study inclusion criteria. Of the five female data sets to be excluded from the data set, one subject dropped out due to lack of motivation, one was dropped from the study for forgetting to take the device on vacation, one individual (bilateral cases) was dropped from the study after re-diagnosis with complex regional pain syndrome Type I, and one subject was excluded when follow-up MRI confirmed a large coexisting haemangioma which may have confounded perception of stress fracture symptoms.

Table 1 is a comprehensive subject list indicating sex, age, primary sport, treatment time in days and recruitment location.

Table 1. Tibial stress fracture subject details.

SUBJECT #	SEX	AGE	PRIMARY SPORT	TREATMENT TIME (days)	LOCATION
1	Female	32	Running	18	Stanford
Excluded	Male	35	Running	19	Stanford
2	Female	46	Running	23	Stanford
3	Female	16	Running	25	Stanford
4	Male	30	Running	14	Stanford
5	Male	22	Running	14	Stanford
6	Male	18	Running	21	Stanford
7	Female	33	Running	18	Stanford
8	Male	19	Running	6	Stanford
Excluded	Female	35	Running	Dropped out	Stanford
9	Female	20	Running	17	Stanford
10	Male	28	Triathlon	24	Stanford
11	Female	21	Running	38	Stanford
12	Male	45	Running	30	Stanford
13	Male	22	Ultimate Frisbee	22	Stanford
14	Male	23	Running	23	Griffith
15	Female	21	Aerobics	2	Griffith
16	Female	18	Sprinting	25	Griffith
17	Female	21	Sprinting	18	Griffith
18	Female	34	Running	37	Griffith
19	Female	18	Running	12	Griffith
Excluded	Female	22	Running	Released from study after failure to use allocated device for an extended period.	Griffith
20	Male	37	Running	7	Griffith
21	Male	37	Running	6	Griffith
22	Male	33	Triathlon	17	Griffith
23	Male	25	Running	8	Griffith
24	Male	25	Running	8	Griffith
25	Female	34	Triathlon	17	Griffith
26	Female	23	Step aerobics	19	Griffith
27	Female	32	Running	17	Griffith
28	Male	21	Boxing/running	15	Griffith
29	Male	21	Boxing/running	16	Griffith
30	Male	42	Running	9	Griffith
31	Male	24	Sprinting	6	Griffith

Table 1 cont

Excluded	Female	24	Netball	Bilateral stress fractures in the same individual, and treated as two cases. Recruited following diagnosis by an orthopaedic surgeon. Released from study after 30 days of intervention and rest from pain-provoking activities as a total lack of change in symptoms was not consistent with the progression of normal stress fracture resolution. She was referred for further evaluation to a sports medicine physician who diagnosed a complex regional pain syndrome Type I.	Griffith
Excluded	Female	24	Netball		Griffith
32	Female	31	Aerobics	22	Griffith
33	Female	31	Aerobics	44	Griffith
34	Male	23	Australian Rules	3	Griffith
35	Male	23	Australian Rules	14	Griffith
36	Female	23	Running	8	Griffith
37	Female	23	Running	8	Griffith
38	Male	24	Australian Rules/ running	11	Griffith
Excluded	Female	32	Netball/ weights	60	Griffith
39	Female	29	Running	21	Griffith
40	Female	21	Running	11	Griffith
41	Female	21	Running	11	Griffith
42	Female	22	Sprinting	13	Griffith
43	Female	22	Sprinting	13	Griffith
44	Female	36	Running/ boxing	26	Griffith

PRIMARY STUDY OBJECTIVES:

- Question 1. Does electric field stimulation and rest from painful weight bearing activity reduce time to recovery from tibial stress fracture in comparison with rest alone?
- Question 2. Is there a gender-specific effect of electric field stimulation on time to recovery from tibial stress fracture?

Details of the primary outcome measures can be found in Appendix 1. The latter is the principal manuscript to arise from the data and, as such, provides a description of the research purpose, methodology, results and conclusions, with descriptive tables summarising subject characteristics and treatment outcomes.

SECONDARY STUDY OBJECTIVES:

- Question 1. Can tibial stress fracture grade classifications on diagnostic images (plain films, bone scan, MRI, CT) predict time to recovery with electric field stimulation?
- Question 2. Is MRI the most sensitive diagnostic imaging technique (compared with plain films, bone scan and CT) for the purposes of identifying tibial stress fracture, and predicting time to recovery from grade of injury severity?

The radiological investigation produced a very large amount of interesting and complex data. Preliminary findings are summarised in Appendix 2. The latter is an abstract submitted for presentation at ACSM in 2007 (New Orleans, LA). Radiological data analyses are ongoing and a manuscript describing a complete interpretation is in preparation.

The radiological grading system was based upon previously published systems (24, 25, 49), and adapted where necessary by the principal study radiologist to reflect the imaging protocols utilised in the current study and advances in knowledge since cited publications (Appendix 3). Not unexpectedly, the imaging modalities differed in their ability to discriminate grade of stress fracture. Table 2 shows the variation in ability of imaging modality to classify grade of tibial stress fracture injury (scored by the principal study radiologist). X-Ray and CT were relatively insensitive imaging modes, while bone scan, and MRI were more discriminating. It is noteworthy that CT grading resulted in the classification of all subjects as either un-injured or relatively severely injured (grade 3), whereas X-Ray never identified more severe cases.

Table 2. Stress fracture subjects categorised according to radiological severity grade for all imaging modalities

Grade	X-Ray		NM bone scan		MRI		CT	
	n	%	n	%	n	%	n	%
0	28	62.2%	4	8.2%	11	24.4%	29	65.9%
1	11	24.4%	17	34.7%	6	13.3%		
2	6	13.3%	24	49.0%	7	15.6%		
3			4	8.2%	20	44.4%	15	34.1%
4					1	2.2%		
Total	45	100.0%	49	100.0%	45	100.0%	44	100.0%

We observed moderate to good inter-grader correlations for all imaging modalities (range: $r = 0.326 - 0.862$, $p < 0.05$, two-tailed) and relatively robust Cronbach's alpha reliability coefficients for the grading system (range: $0.591 - 0.895$).

Bone scan grade predicted time to healing ($R^2 = 0.241$, $p = 0.007$), as did a combined radiology score of all imaging modalities ($R^2 = 0.243$, $p = 0.03$) pooling scores from all graders. No individual graders' scores predicted time to healing from any imaging modality. A

comparison of four discrete tibial stress fracture grades derived from the combined baseline radiology score (grade 1 = 1-3, grade 2 = 4-6, grade 3 = 7-9 and grade 4 = >10), did, however find a significant difference in days to healing between groups ($F = 4.79$, $p = 0.007$), but was underpowered. This difference was found to exist in the placebo group only, suggesting that the effect of electrical stimulation 1. influenced healing and 2. may influence the predictive ability of radiological severity scores.

A range of radiological expertise was purposely enlisted for the purposes of radiological reading to observe the effect of experience on inter-reader correlation and predictive ability of the grading system. That is, two stress fracture expert musculoskeletal radiologists were enlisted, along with a non-expert musculoskeletal radiologist, and a stress fracture specialist orthopaedic surgeon. It was expected that inter-reader correlations would be high between the two expert radiologists, but unknown how the remaining readers would compare. In reality, the level of correlation between all readers was highly variable with respect to imaging modality and expertise. This lack of consistency in reliability is a curious finding and is the subject of detailed ongoing investigation.

Provide data explaining the relationship of the most recent findings with that of previously reported findings.

As the device codes were not unblinded until the final subject data set was collected, early reports from the data were not possible. Primary findings were presented at the 2006 annual meeting of ACSM in Denver, CO. Those data are identical to that reported in the manuscript attached (Appendix 1).

Problems in accomplishing any of the tasks.

Research activities proceeded very smoothly once administrative issues related to award subcontracting from Stanford to Griffith University were resolved. Administration of the subcontract by the Griffith University Office for Research was extremely efficient, and Griffith-Stanford communication was facilitatory.

Support from our industry partner, Bioelectron (now EBI) who provided the OrthoPak devices free of charge was generous and reliable, notwithstanding a takeover and changes in liaising personnel during the award period.

In the initial months of the study, when based at Stanford University it was occasionally difficult to arrange radiological appointments at short notice, but this issue resolved immediately the study was transferred to Griffith University on the Gold Coast, Australia. Griffith University has an exceptional relationship with the local Southcoast Radiology Clinic whose staff were extremely accommodating with scheduling and provided greatly discounted research rates for our radiological examinations.

The logistics associated with the protocol requiring approval from the US Army HSRRB, Stanford University Administrative Panel on Human Subjects in Medical Research (HSMR), Griffith University Human Research Ethics Committee (HREC) and the Australian Defence Force Human Research Committee (ADHREC) were challenging, but manageable. (ADHREC approval was required for subjects to be recruited from the local army base.)

The employment of a research assistant at Griffith facilitated dedicated attention to subject recruitment, which was imperative for the success of the trial. Owing to the nature of a

convenience sample, and as predicted in the original Statement of Work, there were periods when subject recruitment was very slow, but other times when numerous subjects were enrolled simultaneously. For example, in 2002, 11 data sets were collected, in 2003 only 5, but in 2004, 16. An intensive and consistently visible approach was the critical strategy for successful recruitment.

Recommended changes or future work to better address the research topic

Our study design was an appropriately rigorous and logistically manageable approach that we are confident provided a valid answer to our research questions. Data collection, management and analysis were maintained to the highest standard for the duration of the study. We acknowledge, however, the optimal conditions for collecting data can be very difficult to achieve in the clinical setting, and our data was not immune to this effect. That is, controlling for every variable influencing subject data (such as menstrual status, etc.) is highly problematic without recruiting exceptionally large subject numbers.

The most important potential confounding variable was injury severity. Although not a mainstream concept at the time of funding (hence our in-depth, multi-modality grading analysis), it is now more accepted that there are degrees of tibial stress fracture injury severity that differ in clinical progression (35). It is possible that subjects suffering different grades of stress fracture may respond differently to electrical stimulation, as our results indeed suggest. Testing such an effect, however, would require the collection of a much larger study sample to ensure adequate case representation and sufficient random allocation of active and placebo devices in each grade to power the statistical analyses for degree of stress fracture severity. The analysis can be done retrospectively to a certain extent within the current sample, however, small numbers of subjects with more severe grades of injury limit our ability to make strong conclusions. (Figures 1a/b)

Figure 1a. Numbers of treatment group subjects in each stress fracture injury grade by bone scan

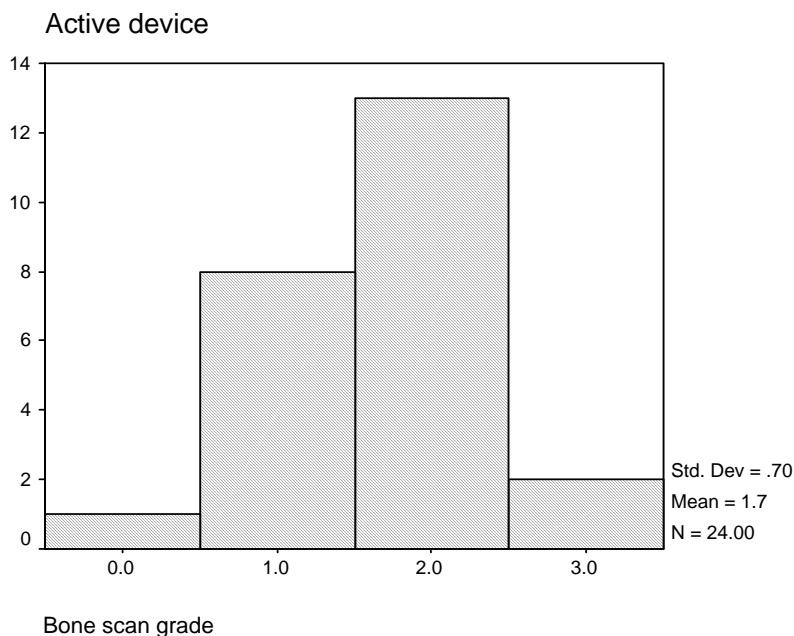
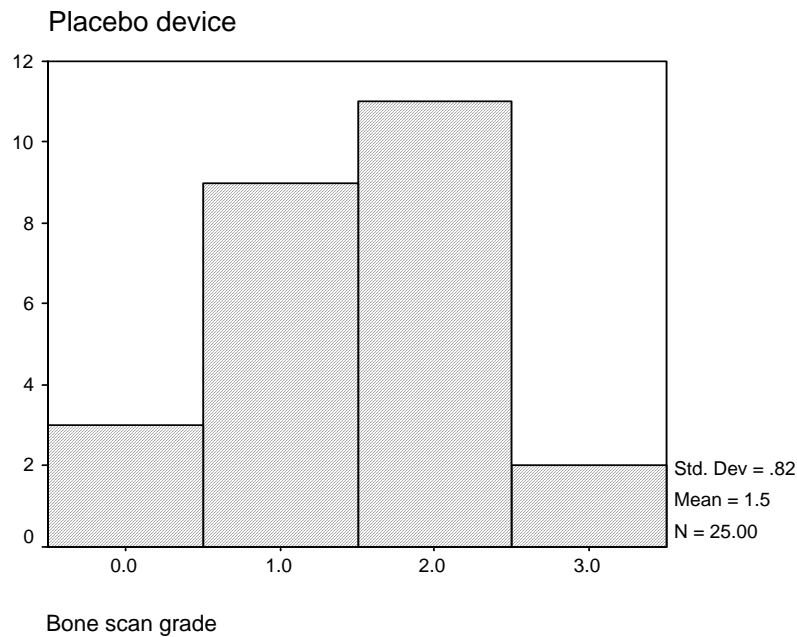


Figure 1 b Numbers of placebo group subjects in each stress fracture injury grade by bone scan (y axis = number of subjects)



Future work

Other devices that have been found to be effective for stimulating regular fracture healing remain relatively untested for stress fracture application. One example is low intensity pulsed ultrasound (LIPU)(39). We plan to examine the effect of LIPU on tibial stress fractures in the future, taking into account severity of stress fracture injury. One previous study examining the effect of LIPU on tibial stress fracture did not consider the effect of injury severity and were unable to detect an effect of the device (42). The authors' findings, like ours, may reflect the confounding influence of injury severity on device efficacy. A large randomized controlled trial to examine the ability of electric field stimulation to accelerate healing in comparison with LIPU according to tibial stress fracture grade could simultaneously answer remaining questions of efficacy of both forms of stress fracture healing stimulation.

KEY RESEARCH ACCOMPLISHMENTS:

- Capacitively coupled electric fields and rest from painful weight bearing activity did not reduce time to recovery from tibial stress fracture in comparison with rest alone
- Superior treatment compliance may enhance the efficacy of electric field stimulation on time to healing of tibial stress fracture
- Minimising weight bearing activity during recovery may also reduce time to healing with electric field stimulation
- There was no gender-specific effect of electric field stimulation on time to recovery from tibial stress fracture
- Women healed more slowly from tibial stress fracture than men regardless of device allocation
- Tibial stress fracture grade by bone scan, but not X-Ray, MRI or CT predicted time to recovery with electric field stimulation
- MRI may be the most sensitive diagnostic imaging technique (compared with plain films, bone scan and CT) for the purposes of distinguishing grades of tibial stress fracture injury, but did not predict time to healing from assigned grade

REPORTABLE OUTCOMES:

Manuscripts:

Submitted:

1. Beck B. R., Matheson G., Bergman G., Hoffman A., Norling T. and Marcus R.: Do capacitively coupled electric fields accelerate tibial stress fracture healing? *Journal of Orthopaedic Research*

In preparation:

2. Beck B.R., Bergman G., Arendt E, Miner M., Klevansky A., Matheson G., Hoffman A., Norling T., and Marcus R.: The relationship of radiological findings to tibial stress fracture healing. Intended for *Radiology*
3. Beck B.R., Bergman G., Arendt E, Miner M., Klevansky A., Matheson G., Hoffman A., Norling T., and Marcus R.: A grading system for tibial stress fracture: X ray, Triple phase technetium bone scans MRI and CT. Intended for *Radiology*.

Abstracts:

1. Beck B. R., Matheson G., Bergman G., Hoffman A., Norling T. and Marcus R.: Do capacitively coupled electric field accelerate tibial stress fracture healing? *Medicine and Science in Sport and Exercise*, 31(5, Suppl. 1): 2006
2. Beck B.R., Bergman G., Arendt E, Miner M., Klevansky A., Matheson G., Hoffman A., Norling T., and Marcus R.: Comparison of Imaging Modalities for Evaluating Injury Severity and Predicting Recovery from Tibial Stress Fracture *Medicine and Science in Sport and Exercise*, 31(5, Suppl. 1): 2007 (submitted)

Presentations:

1. *Stimulating Bone: Current options.* Orthopaedic Nurses Conference, Brisbane, Nov 5, 2004 (Invited state of the art talk. Did not report research outcomes.)
2. *Electric field stimulation of stress fracture.* Australian Physiotherapist Association State Conference, Toowoomba, QLD, August 1-3, 2003 (Invited mechanistic talk. Did not report research outcomes.)

CONCLUSIONS:

Capacitively coupled electric fields did not accelerate the rate of tibial stress fracture healing compared with placebo treatment. We note, however, that increased device use and rest compliance improved the efficacy of the electric field stimulation, and that such improvements (however small) may be significant for individuals requiring especially rapid return to training or competition. The healing of more severe tibial stress fractures appeared to benefit from electric field stimulation, however, our sample was not fully powered to confirm the observation. Future work to address an injury grade-specific effect is recommended.

A combined baseline radiology score of injury grade from X-Ray, Triple phase technetium bone scans MRI and CT predicted time to healing, but no better than bone scan grade alone.

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APPENDIX 1:

Manuscript prepared to report primary study outcomes (Submitted, JOR)

Title

Do capacitively coupled electric fields accelerate tibial stress fracture healing? A randomized, controlled trial.

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Running title Electric field stimulation of stress fracture

Summary

Purpose: To determine the effect of capacitively coupled electric field stimulation on tibial stress fracture healing in men and women.

Methods: A convenience sample of 20 men and 24 women with posteromedial tibial stress fractures was recruited. Subjects were randomly assigned an active or placebo OrthoPak[®] Bone Growth Stimulator (sinusoidal wave, 3-6 V, 60 kHz, 5-10 mA), to be used for 15 hours per day until healed. Subjects were given supplemental calcium and instructed to rest from training. Healing was confirmed when hopping 10 cm off the ground for 30 seconds was painfree. Data was analysed using 2-way ANOVA for effects of treatment and sex on healing time. Compliance and other between-group differences and relationships were examined via ANOVA, t-tests and correlation analyses. The influence of anthropometric and behavioural characteristics on time to healing was evaluated by multiple regression analysis.

Results: No difference in time to healing was detected between treatment and placebo groups. Treatment compliance was positively associated with reduced time to healing ($p = 0.003$). Rest non-compliance was associated with increased time to healing ($p = 0.05$). Female subjects healed more slowly than men ($p = 0.05$).

Conclusions: Capacitively coupled electric fields did not accelerate tibial stress fracture healing in comparison with placebo treatment (modified rest), but women took longer to recover than men. Daily device use and weight bearing loading during treatment appeared to positively and negatively (respectively) influence the effect of the active device.

Keywords: CLINICAL TRIALS; BONE STRESS INJURY; TREATMENT - NOVEL ENTITIES; ELECTRIC FIELD STIMULATION; SPORTS INJURY

Introduction

Stress fractures are focal structural weaknesses in bone occurring with the repeated application of sub-frank fracture-threshold stress (17). Stress fractures typically result from chronic skeletal overloading occurring over a period of time that is inadequate to allow appropriate bone adaptation. They are increasingly common injuries in athletic and military populations, and thought to affect more female army recruits than male (5, 26).

With some exceptions, fractures of this nature heal spontaneously if the injury site is relieved for a time from the aggravating loading. The period of time required for healing to occur with rest, however, can be quite prolonged. The most common site of stress fracture is the tibia (6). A comprehensive review of the literature reveals that an average of 12 ± 7 weeks rest has been recommended for the resolution of tibial stress fractures. Such a lengthy duration is highly problematic for athletes in critical training or competitive periods, for army recruits engaged in 14-week basic training courses, and for individuals simply attempting to maintain a level of fitness for health benefits.

Few treatments to enhance the rate of stress fracture healing have been empirically tested, and of those that have, results have been disappointing or equivocal. For example, the use of a pneumatic leg brace was reported to enhance the rate of healing in a small ($n = 18$) athlete study (47), but not in a larger ($n = 31$) controlled study of soldiers with tibial stress fractures (1).

Electric fields are known to activate the bone formation process *in vitro* (29). Furthermore, electric and electromagnetic field stimulation has been shown to facilitate the healing of recalcitrant fractures in humans, *in vivo* (44-46). The rationale for the current study was based on the assumption that, as bone repairs via an essentially similar mechanism regardless of the nature of the fracture, electric field stimulation should similarly promote healing of stress fractures. Some preliminary evidence exists to support such an hypothesis (4), however, no controlled, randomised trial has previously been conducted to appropriately test the theory.

The current study objective, therefore, was to examine the effect of capacitively-coupled electric field stimulation versus placebo treatment on rate of tibial stress fracture healing in men and women via a double-blind, randomised, controlled trial. A capacitively coupled electric field (CCEF) device that operates with signal parameters known to stimulate osteoblasts and designed to optimise patient compliance was selected to deliver the intervention stimulation (OrthoPak[®] Bone Growth Stimulator Systems, FDA approved for non-union fractures; EBI, formerly Bioelectron, Inc., Hackensack, NJ).

Methods

The study was approved by the US Army Human Subjects Research Review Board, the Stanford University Panel on Human Subjects in Medical Research, the Griffith University Human Research Ethics Committee, and the Australian Defence Human Research Ethics Committee.

Sample size and power

Women and men between the ages of 18 and 50, recently diagnosed with one or more tibial stress fractures, were recruited from the San Francisco Bay area (California, USA) and the Gold Coast region (Queensland, Australia) over a period of seven years. Power calculations (based on a predicted effect size of 3 weeks, $s = 4$, $\alpha \leq 0.05$, and $\beta = 0.80$) indicated a total of 32 subjects (8 in each of 4 groups) was required to detect between-group healing differences according to both device status and sex. We chose to recruit additional subjects to avoid any group shortfalls consequent to convenience sampling, aiming for a total of 40 subjects, 20 men and 20 women. Our figures were derived from the consideration that a healing time difference of three weeks would constitute a practically worthwhile effect, based on literature reports of an average time to tibial stress fracture healing of 12 weeks. Ultimately, power to detect differences between treatment and placebo groups based on real subject numbers and healing times was 95.7%, and power to detect differences between male and female responses was 100% for the 95% confidence interval.

Subject selection

Eligibility for the study was based on the presence of one or more acute tibial stress fractures, for which no significant treatment, aside from rest, had been prescribed. Only posteromedial mid to distal third and proximal medial tibial stress fractures were investigated. Mid anterior tibial shaft stress fractures were excluded, being of dissimilar aetiology to typical tibial stress fractures, and particularly prone to delayed- or non-union (16). Subjects were excluded from the study if they were pregnant, used a pacemaker, had a metabolic bone disease, or took medication known to influence bone healing.

Clinical Diagnosis

Patients diagnosed with tibial stress fractures were referred to study investigators from their sports medicine clinician. Study personnel then performed a comprehensive injury assessment to standardized evaluation criteria. The diagnosis of stress fracture was determined according to patient history and the presence of significant

focal tenderness at either of the above described sites that was most pronounced when the affected limb was loaded. Intensity of signs and symptoms including: tenderness, night pain, pain with percussion, localized bone swelling, spongy texture overlying the injury, and warmth at the site, were recorded on a scale of 1-3. A “clinical severity score” was calculated by the addition of all sign and symptom scores for a possible total out of 21.

Diagnostic Imaging

Although eligibility for study enrollment was based exclusively on clinical diagnosis, a comprehensive series of imaging examinations was ordered for each subject to obtain further information regarding injury severity. Plain X-rays have poor diagnostic sensitivity to stress fracture, detectable changes often lagging two to six weeks from onset of symptoms, however, they were obtained in order to standardize findings and rule out unforeseen pathology. Triple phase technetium bone scans are highly sensitive to bone stress reactions and were thus used to confirm injury site and severity. Presently considered the gold standard for stress fracture diagnosis, magnetic resonance images were taken at baseline and follow-up in order to more precisely observe location(s) and degree of local swelling. Although not widely used, computed tomography has also been reported for stress fracture imaging, and thus was included in the radiological protocol for the current study.

Severity of injury was graded on a scale of 1-4 for each method of imaging. A “radiological severity score” was calculated by the addition of imaging scores for each modality for a possible total out of 16. The total radiological severity score was stratified into four injury grades (grade 1 = 1-3, grade 2 = 4-6, grade 3 = 7-9 and grade 4 = >10) to approximate the stress fracture grading systems recently reported in the literature (2, 21, 24, 25, 49). The low-end range of the stratification was emphasised to account for the low sensitivity of plain films and CT, and the consequent likely small contribution of those scores to the overall radiological severity score.

All images were blinded and graded independently by musculoskeletal radiologists on separate occasions in order to evaluate inter-reader reliability. A complete report of the radiological analysis will be reported elsewhere.

Subject characteristics

A comprehensive record of relevant physical and behavioural characteristics was collected (age, height, weight, medical history, training patterns, orthopaedic abnormality, menstrual status, etc). Each subject completed a National Cancer Institute Health Habits Food Frequency Questionnaire (Block Dietary Systems, San Francisco) to determine average daily calcium consumption in milligrams. Subjects were provided with calcium supplements (*TUMS 500 Chewable*, 500 mg calcium carbonate, SmithKline Beecham) and instructed to consume one supplement

per day to ensure adequate calcium availability during the course of the intervention. All subjects were examined by dual energy x-ray absorptiometry to determine bone mineral density at the whole body, proximal femur, lumbar spine and forearm. A bone mass score was derived for each subject by calculating the average z score from all regions.

Treatment

Active and inactive (placebo) OrthoPak® Bone Growth Stimulator Systems (EBI, Hackensack, NJ), were provided coded and blinded to investigators by the manufacturers. An active OrthoPak® device is a small, portable, capacitively-coupled electric field (CCEF) stimulator that applies a sinusoidal wave of 3 - 6 V at 60 kHz and 5 - 10 mA via two adhesive, water-based gel electrodes (Figure 1).

Once diagnosed, and baseline data collection was complete, each subject was immediately assigned an OrthoPak® unit with replacement 9 Volt batteries and electrodes, and the intervention initiated. Subjects were instructed to use the OrthoPak® for 15 hours per day, to replace the battery every morning, and to keep the device alarm switched on. The alarm would sound if electrode contact was lost from the skin or battery power was low, an event signalling that the electric field had been interrupted. A daily treatment record log was provided for subjects to record actual hours of use and any side effects or exercise activity they undertook. OrthoPaks® were issued according to sequential serial number, as device status had been randomized in this order. Active and inactive OrthoPak® units looked and ostensibly functioned in the same manner, and all subjects were treated identically.

All subjects received standard stress fracture rehabilitation advice in order to avoid treatment withholding from the placebo group. Regular rehabilitation primarily consisted of rest from any painful activity. In-saddle stationary cycling and pool running were acceptable training alternatives to repetitive weight bearing training. Crutches were available for subjects unable to perform activities of daily living without pain, but this was never the case. Subjects were issued with acetaminophen (Tylenol Extra Strength Gelcaps, 500 mg, McNeil Consumer Products, Fort Washington, PA, USA) and asked to avoid NSAIDS. No subject reported use of any form of pain medication during the course of the study.

Subject monitoring

Participants were contacted by phone or email every second day for a progress report (rating signs and symptoms from 1 – 3). Running was not attempted until subjects were pain free with walking, and hopping was not attempted until subjects were pain free with running (50 meters).

When a complete absence of pain during hopping on the affected limb for 30 seconds to a height of 10 centimetres off the ground was reported and confirmed by investigator examination, the subject was considered healed and the intervention ceased. Participants then received a follow-up MRI examination and returned their completed treatment log and OrthoPak[®] to investigators. The device was tested using the manufacturer-provided “Physician Test Meter” which detected days of use in 24 hour periods. A functional measure of healing was deliberately chosen as the outcome measure, rather than appearance on follow-up imaging, in order to standardize the dependent variable to a practical benchmark and reflect usual practice for stress fracture management in the clinical setting. No standardized system of classification to confirm stress fracture healing on MRI was available at study inception.

Statistical analysis

Statistical analyses were based on intention to treat. The effect of subject compliance was examined in specific analyses described below.

Device effect was evaluated via two-way ANOVA to determine if differences existed in time to healing between active and placebo treated subjects, and between men and women. In order to account for variation between subjects in duration of injury before study enrollment, the analysis was run for both the time between date of injury and healing, and the time between initiation of intervention and healing. A further analysis was run to examine actual treatment time (time the device was worn) according to the Physician Test Meter. The latter varied from number of days to healing as subjects were instructed to use the device for only 15 hours per day.

To determine if severity of injury affected time to healing, a number of severity indices were also compared with outcome measures. Two-way ANOVA was used to compare time to healing using device status and clinical severity score as factors. Time to healing was also compared via two-way ANOVA using device status and radiological severity score as factors. Finally, time to healing according to tibial stress fracture injury grade (1-4) was compared via one-way ANOVA for the whole group and using a split file analysis for device status.

The effect of subject compliance with intervention instructions on treatment time was similarly examined via two-way ANOVA. One model examined actual hours of device use (from the Physician Test Meter) per number of real treatment days, i.e. treatment compliance, versus device status. Device use compliance was examined more closely by way of a t-test comparison of subjects who complied >70% with those who complied <70% using Physician Test Monitor hours to healing as the dependent variable. Further, a split file (according to device status)

correlation analysis of days to healing from start of treatment versus device use compliance was performed. A second compliance model used a rating assigned to level of weight bearing activity (derived from number and intensity of exercise bouts during the intervention period) recorded in the subject log during treatment, i.e. rest compliance, versus device status.

The effects of subject physical, behavioural and injury characteristics on time to healing (age, sex, height, weight, body mass index - BMI, fracture site, delay from injury to start of intervention, daily calcium consumption, clinical injury severity, radiological injury severity, menstrual status, oral contraceptive use, percent fat, percent lean mass, bone mineral density, calcaneal broadband ultrasound attenuation - BUA, rest compliance, and device use compliance) were tested via stepwise multiple regression for the group as a whole, and in split-file analyses according to either sex or device status.

Correlation analyses were examined to observe the nature of specific relationships between time to healing and variables such as injury severity or delay to treatment start.

Results

A total of 50 tibial stress fracture treatments were initiated, of which 44 (20 male, 24 female) were completed. Twenty-three of the randomly allocated devices were active (9 to men, 14 to women), and 21 were placebo (11 to men, 10 to women). Subjects excluded from the final analysis included four misdiagnoses (one anterior tibial stress fracture, one hemangioma, two cases of complex regional pain syndrome Type I), and two subjects released from the study for failure to initiate the protocol.

All statistical analyses satisfied Levene's test for homogeneity of variance for between group comparisons.

Subject characteristics are summarised in Table 1. Subjects were primarily involved in running and running-related activities. Treatment versus placebo group comparisons revealed no subject characteristic differences with the exception of percent fat (active > placebo, $p = 0.02$) and percent lean mass (active < placebo, $p = 0.03$). Within sex, there were no differences between treatment and placebo groups with the same body composition exceptions. Women allocated an active device had significantly greater percent body fat ($p = 0.02$) and less lean mass ($p = 0.03$) than women issued a placebo device. Between sex group comparisons reveals predictable differences in height, weight, BMI, percent fat, percent lean mass and BUA, men being significantly taller and heavier with lower percent fat than women. Men consumed greater amounts of calcium than women (1391.7 ± 689.1 vs 958.1 ± 359.9 mg, $p = 0.02$).

A summary of healing times, injury severity ratings and compliance scores is presented in Table 2. There were no differences in severity of injury between treatment and placebo groups, whether assessed clinically or radiologically. There were no differences in treatment compliance (number of hours per day of device use) between treatment and placebo groups, nor in degree of compliance with the instruction to rest from weight bearing activities during treatment. Similarly, no between-sex differences existed in any compliance or injury severity variable.

Two-way ANOVA to examine the main effects of device status and sex indicated there was no difference in time to healing from the start of treatment between active device (27.7 days) and placebo-treated subjects (25.9 days), but that women healed more slowly (31 days) than men (22 days) ($p = 0.05$). There was no interaction effect. No main effect was detected for either device status or sex when the analysis was run for the time between date of injury and healing, or actual treatment time (time the device was worn) according to the Physician Test Meter.

The effect and interaction of treatment compliance on time to healing, according to device status was examined by running specific two-way ANOVAs using: (i) treatment compliance (actual hours of device use per number of real treatment days), and (ii) rest compliance (amount of weight bearing activity during treatment) as factors, in combination with device status. Two main effects were revealed. Greater engagement in weight bearing activities during treatment increased the time to healing from the start of treatment for subjects using the active device in comparison with placebo users ($F = 2.583$, $p = 0.05$). Increased hours of device use per day was associated with greater reduction in time to healing (measured by the Physician Test Meter) in the treatment group than the placebo group ($F = 57.533$, $p = 0.003$). The split file correlation analysis similarly indicated a significant inverse relationship between time to healing and device use compliance for subjects allocated an active device ($r = -0.355$, $p = 0.05$), but no relationship for placebo allocated subjects ($r = -0.009$, $p = 0.972$). The t-test comparison revealed a significant difference between time to healing (in Physician Test Meter hours) of subjects who complied $>70\%$ (used the OrthoPak[®] for >12.25 hours/day) compared with those who complied $<70\%$ ($t = 2.739$, $p = 0.009$, 95% CI 2.07, 13.797).

The effect and interaction of injury severity on time to healing, according to device status was examined by running specific two-way ANOVAs using: (i) clinical injury severity, (ii) radiological injury severity as factors, in combination with device status. No differences in time to healing could be detected from these analyses. A direct comparison of time to healing according to injury grade (1-4, described above), however, revealed significant between-group differences ($F=4.79$; $p = 0.007$). When a split file analysis was run according to device status, time

to healing differed between subjects of different injury grades only if they were allocated a placebo device ($F = 11.08$; $p = 0.001$). A t -test comparison of healing times of subjects with a bone scan severity grade >2 versus ≤ 2 likewise showed no differences in healing time between subjects allocated an active device (23.5 ± 16.3 vs 31.2 ± 22.0 days), but a significant difference in healing time for similarly injured subjects allocated a placebo device (48.0 ± 36.8 vs 24.4 ± 8.7 days, $p=0.01$). These figures indicate that grade 3 and 4 tibial stress fractures treated with an active device healed 24.5 days faster than those allocated a placebo device. It is important to note that these analyses are not sufficiently powered to make definitive conclusions owing to the small number of subjects classified >2 in bone scan severity grade.

Correlation analyses revealed no significant relationships between time to healing and variables such as injury severity or delay to treatment start. One exception was a split file analysis for device status that reconfirmed a significant positive relationship between radiological injury severity and time to healing from date of injury for subjects issued placebo devices (Pearson's $r = 0.456$, $p = 0.03$).

Whole group multiple regression analyses of the effects of subject physical, behavioural and injury characteristics confirmed that female sex predicted 27.7% of the variation in time to healing from start of treatment ($F = 5.746$, $p = 0.03$). Weight (50.5%, $p = 0.007$) and rest non-compliance (67.8%, $p = 0.002$) accounted for the majority of the remaining variation.

Split-file analyses according to sex and device status revealed some subtle differences according to group. For the treatment group, percent lean mass predicted 66.5% of the variation in treatment time ($F = 9.928$, $p = 0.025$) with no other variable contributing significantly to the remainder of the variation. For the placebo group, fracture site predicted 99.5% of the variation in treatment time ($F = 400$, $p = 0.002$). When analysed according to sex, present use of oral contraceptives predicted 61% of the variation in treatment time for women ($F = 14.074$, $p = 0.005$), with delay to start of treatment (80.1%, $p = 0.002$), BUA (90.1%, $p = 0.001$) and menstrual status (97.5%, $p = 0.00006$) accounting for the majority of the remainder of the variation. The same analysis for men, excluding female-specific covariates, revealed that radiology injury severity grade predicted 90.3% of the variation in treatment time ($F = 37.425$, $p = 0.004$) with clinical injury severity grade (97.8%, $p = 0.003$) accounting for the majority of the remainder of the variation.

Discussion

Our goal was to rigorously examine the effect of capacitively-coupled electric field stimulation on rate of stress fracture healing by controlling stress fracture site, including both male and female subjects and employing a double-blind, randomised, controlled design.

A direct, between-group comparison suggests that there were no differences in rate of healing between treatment or placebo groups, but that men healed on average nine days faster than women from the initiation of treatment. The lack of detectable between-group differences in injury severity, treatment compliance, and delay to start of treatment from injury date suggest that some characteristic or behaviour related to sex may be a more powerful influence on stress fracture healing than the application of electric fields. The observations that use of oral contraceptives and menstrual status account for variation in time to healing for women, and that male subjects consumed significantly more calcium than females, support such a contention.

Closer scrutiny of the data, however, suggests that an effect of electric field stimulation on stress fracture healing did exist. For example, increased hours of device use per day reduced time to healing in the treatment group but not the placebo group. In addition, participation in weight bearing activities had a more negative effect on time to healing in subjects treated with an active device than on placebo users. These observations, and the contribution of rest non-compliance to explaining variation in time to healing in the whole group regression model, are suggestive that treatment compliance influences the effectiveness of CCEF stimulation for tibial stress fracture healing.

It is notable that, retrospectively, greater radiological injury severity was consistently associated with an increased time to healing in the placebo group, but not the treatment group. That stress fracture injury grade appeared to influence rate of healing most in our placebo group is suggestive that CCEF stimulation may be indicated for more severe grades. In order to prospectively test the hypothesis that tibial stress fracture injury grade influences the efficacy of CCEF, future investigations must recruit additional cases to ensure adequate numbers in each grade category (grades 1-4) to maximize statistical power for cross grade comparisons.

Electrical stimulation has been used sporadically by clinicians for over a century. In 1820, Mott (36) used electricity to heal non-union fractures and Lente (31), in 1850, described healing three cases of delayed unions in this manner. More recently, empirical evidence has indicated that electric and electromagnetic fields effect responses from bone cells in culture (9, 10, 18, 29, 41). Clinical effects such as the stimulation of bone graft, spine

fusion, osteotomy and non-union healing (12, 14, 27, 34, 45), and the prevention of disuse osteopenia (8, 40), have also been reported.

To date, only one study has investigated the effects of electric field stimulation on stress fractures (4). Of twenty-five stress fractures treated with CCEF (3.0 - 6.3 V, 60 kHz) for an average time of 7.4 weeks (navicular - 8.6 weeks), 88% healed, 8% improved and 4% did not heal. As the average time between stress fracture symptom onset and beginning treatment was 21 weeks (navicular - approximately 32 weeks), time to healing with the addition of electric field stimulation was a substantial improvement (13 and 24 weeks) on healing without stimulation. While the results were encouraging, the study controlled for neither a placebo effect, nor stress fracture type or prior healing.

Although all create potentially effective electric fields in tissue, CCEF has distinct advantages over direct current (DC) or pulsed electromagnetic field (PEMF) stimulation of bone. DC stimulation is an invasive approach, necessitating surgery. PEMF generates a magnetic field from which an electric field is produced, losing power in the process. As current from the rigid, unwieldy coil diminishes rapidly with distance, a heavy power supply requiring daily recharging is needed. A CCEF device, by contrast, is small and light weight (4 oz); using a 9Volt battery. Small, flexible, gel electrodes adhere to any anatomical site and couple the current directly to the skin, producing a wide stimulatory field close to the fracture site with little loss of power. Furthermore, CCEF stimulates significantly more DNA production from bone cells than PEMF (15). The difference in effect is likely due to different mechanisms of action, the latter being reliant on activation of finite intracellular stores of calcium while the former (CCEF) can utilise the infinite amount of calcium available in the extracellular space (15).

The signal parameters of the OrthoPak[®] were derived from the results of animal studies comparing the effects of various CCEF parameters (voltage, current and frequency) on healing of fresh osteotomised rabbit fibulae (7). Signal frequency must be greater than 10kHz to penetrate the electrode-epidermis interface (19). A(48) very low voltage (60kHz) signal was found to be optimal for osteochondrogenesis in the rabbit fracture model (7). A voltage dose-response effect has been observed, with 5 volts peak to peak optimising growth acceleration in growth plates (11).

The transduction mechanism proposed to mediate a proliferative response from bone cells *in vitro* following CCEF involves the membrane translocation of calcium via voltage-gated calcium channels (15). Activation of phospholipase A₂ in the cell membrane causes an increase in prostaglandin E₂ (32, 33) which

stimulates osteoblast proliferation (23). Increased cytosolic calcium leads to an increase in activated calmodulin (15), which is known to promote nucleotide synthesis and cellular proliferation (22). It is as yet unknown whether the *in vitro* mechanism is representative of the *in vivo* process.

It is known that whole bone deformation creates negative potentials on the concave or compressed surfaces of bone, and positive potentials on tensile surfaces (3, 30). The preponderance of recent evidence indicates the effect is a consequence of streaming potentials (28, 37, 43), the voltage differences observed between two points of a charged substance through which an electrolyte is forced. *In vivo*, flow of fluid in the canalicular spaces during bone loading exposes osteocytes and bone lining cells to two physical forces, one electrical (streaming potentials) and one mechanical (shear). As bone tends to be deposited at sites of negative charge, for a time it was theorized that streaming potentials transduced the mechanical load signal to bone cells (3).

In fact, it is most likely that fluid flow transduces mechanical signals and that streaming potentials, are an epiphenomenon, that is, a measurable consequence of, but secondary to fluid flow, in this respect. Membrane shear stress, a tangential force generated by adjacent viscous fluid flow, can stimulate bone cell metabolism. The physical deformation of osteoblast membranes is known to reorganise the cytoskeleton and increase expression of cyclooxygenase-2 following inositol-triphosphate-mediated intracellular calcium release(20, 38), with a similar increase in activated calmodulin that is observed with CCEF stimulation (13, 15). Thus, it is conceivable that electric field stimulation of bone achieves its effect by way of fluid flow electroosmosis, an electrokinetic relative of streaming potentials. That is, flow of the electrolytic bone fluid may arise as a consequence of the application of an electric field to bone. While the observed electrochemical membrane effects of CCEF are convincing(15), it is possible that both electrochemical and mechanical mechanisms are involved.

The lack of generalised effect of the OrthoPak[®] to accelerate healing in our cohort may arise from an intrinsic threshold rate of stress fracture healing below which extrinsic stimuli fail to promote further affect. It is noteworthy that previous reports of the time required for tibial stress fracture healing of 12 ± 7 weeks (84 days) grossly exceeds the average time taken for current study subjects to heal (roughly 26 days from treatment initiation or 54 days from injury), regardless of device allocation status. It is possible that the close monitoring of subjects, the constant encouragement to minimise weight bearing training during treatment, the provision of calcium supplements, and the discouragement from ingesting NSAIDS, optimised rate of healing for all subjects. Under such conditions, subtle differences in healing speeds become very difficult to detect, and arguably clinically

insignificant. This would likely not be the case for more exceptional fractures (frank, non-unions and pseudarthroses) for which healing times are more prolonged, and significant CCEF efficacy has been reported.

While we can conclude with some certainty that female subjects took longer to recover from tibial stress fractures than male, based on direct between-group comparisons, we cannot conclude that treatment with CCEFs accelerates tibial stress fracture healing. Still, our compliance and injury severity observations are compelling. We observed positive effects of device use compliance, and a negative influence weight bearing loading during treatment; both modifiable behaviours. We also noted that the effect of severity of injury on days to healing was less marked on our stimulated subjects suggesting CCEF may be indicated for higher grades of tibial stress fracture. Our intention to treat analysis should reflect real-life efficacy of CCEF stimulation on tibial stress fracture healing of the average individual. It is possible, however, that the higher stakes associated with healing for elite or more severely injured athletes may inspire superior treatment compliance, and render CCEF stimulation an effective treatment option when even minor reductions in days to healing could mean the difference between an ability or inability to compete in a once-in-a-lifetime event.

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Manuscript Table 1. Characteristics of stress fracture subjects treated with active and placebo electric field stimulation

Characteristic	Male (n = 20)				Female (n = 24)			
	Active (n = 9)		Placebo (n = 11)		Active (n = 14)		Placebo (n = 10)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Age (yrs)	28.33	2.56	26.09	2.41	27.79	2.12	23.90	1.97
Height (cm)	178.17	1.81	178.60	2.29	164.69	1.31	166.05	2.20
Weight (kg)	78.25	2.78	80.54	2.38	61.04	2.57	57.41	1.48
Body Mass Index (kg/cm ²)	24.65	0.80	25.26	0.64	22.56	1.01	20.83	0.45
Daily calcium intake (mg)	1543.3 ^c	268.4	1432.1 ^c	244.6	1013.2	117.0	881.0	65.7
Percent fat	18.4	2.1	15.7	2.2	33.8	2.4	25.1 ^a	1.9
Percent lean mass	78.3	2.0	80.5	2.1	62.6	2.3	70.4 ^b	1.9
BUA (dB/MHz)	102.6	5.7	114.2	9.5	92.0	5.8	93.8	5.6
BMD composite (z score average)	0.73	0.52	0.88	0.40	0.55	0.38	-0.26	0.24

a Female Active > Placebo, p = 0.02, b Female Active < Placebo, p = 0.03, c Men > Women, p = 0.02. BUA - broadband ultrasound attenuation, BMD - bone mineral density

Manuscript Table 2. Stress fracture subject treatment times, healing rates, injury severity and compliance scores

	Male (n = 20)						Female (n = 24)					
	Active		Placebo		Group Total		Active		Placebo		Group Total	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Time to healing from start of treatment (days)	18	5	25	3	22	3	34	4	27	6	31 ^a	3
Time to healing from injury date (days)	52	10	42	7	47	6	67	9	55	8	61	6
Treatment time (Test Meter 24 hr periods)	10	2	15	2	13	1	19	3	17	3	18 ^b	2
Clinical injury severity (pain) score	11.07	1.61	12.81	0.91	12.03	0.88	13.26	0.86	13.91	0.79	13.53	0.59
Radiological injury severity score	4.86	0.59	5.50	0.75	5.24	0.50	4.31	0.50	6.14	1.08	4.95	0.52
Delay to begin intervention (days)	34	8	18	5	25	5	33	8	27	6	31	5
Device use compliance (Physician Test Meter hours/treatment days)	13.52	1.94	16.97	1.64	15.34	1.29	14.04	1.36	15.66	1.12	14.66	0.94
Rest compliance (Degree of continued weight bearing activity)	1.1	0.3	1.2	0.2	1.1	0.2	1.0	0.2	1.3	0.3	1.1	0.2

a Females > males (p = 0.04), b Females > males (p = 0.05)

Manuscript Figure 1. The OrthoPak® Bone Growth Stimulator System in situ for the treatment of a mid-to-distal third posteromedial tibial stress fracture



APPENDIX 2

Abstract submitted in November 2006 for presentation at the 2007 meeting of the ACSM, New Orleans, LA., USA

Comparison of Imaging Modalities for Evaluating Injury Severity and Predicting Recovery from Tibial Stress Fracture

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Plain X-ray, triple phase technetium⁹⁹ polyphosphonate bone scan (BS), magnetic resonance imaging (MRI) and/or computed tomography (CT) have been used to evaluate stress fracture. Multiple method imaging is expensive and may expose patients to unnecessary radiation, to minimal clinical advantage. There is a need to establish guidelines for the most appropriate imaging modality to diagnose and prognosticate stress fracture injury.

PURPOSE To identify the imaging modality that best predicts tibial stress fracture severity and recovery time.

METHODS A convenience sample of 50 patients with tibial stress fracture was recruited. Subjects were examined acutely on the same or subsequent days via standard AP and lateral radiographs, BS, MRI and CT. A repeat MRI was obtained within 3 days of healing (asymptomatic with hopping). Examinations were graded on 0-4 modality-specific severity scales by 4 reviewers (2 stress fracture-specialist musculoskeletal radiologists, 1 non-specialist musculoskeletal radiologist, and 1 stress fracture-specialist orthopaedic surgeon). The relationships of image grade to clinical severity and time to healing were examined via correlation analyses. The predictive abilities of each imaging modality were examined via multiple regression analyses. The reliability of the grading system was evaluated via repeated measures ANOVA and Cronbach's alpha coefficient.

RESULTS Despite moderate to good inter-grader correlations for all imaging modalities (range: $r = 0.326 - 0.862$, $p < 0.05$, two-tailed) and robust Cronbach's alpha reliability coefficients for the grading system (range: $0.591 - 0.895$), no imaging modality consistently predicted tibial stress fracture clinical injury severity. When only two graders were included in the regression model, however, BS grade predicted clinical severity ($R^2 = 0.138$, $p = 0.03$). BS grade also predicted time to healing ($R^2 = 0.241$, $p = .007$), as did a combined radiology score of all imaging modalities ($R^2 = 0.243$, $p = 0.03$) including all graders.

CONCLUSION Tibial stress fracture clinical severity bears poor relationship to the appearance of severity on diagnostic imaging. BS was the most effective imaging modality for tibial stress fracture prognostication.

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Category = 1001 Athlete Medical Evaluation and Care

APPENDIX 3

Grading system developed and/or adapted to evaluate severity of tibial stress fracture injury for subjects recruited into the current study

Grade	X Ray	NM (modified from Zwas et al., 1987)	MRI (modified from Gaeta)	CT (with reference to Gaeta et al, 2005)
0	No abnormality	No abnormality	No abnormality	No abnormality
I	Grey cortex sign. Margin is indistinct and density is lower.	Linear increased activity in the cortical region	Mild to moderate periosteal oedema on T2-weighted images only with no focal bone marrow abnormality	Soft tissue mass adjacent to periosteal surface
II	Periosteal reaction – clearly acute – density difference from rest of cortex showing incomplete mineralisation	Small focal region of increased activity	Periosteal oedema and bone marrow oedema on T2 only	Increased attenuation of yellow marrow
III	Lucent areas in cortex, ill-defined foci at site of pain	Larger focal lesion with highly increased activity in the cortical region	Marrow oedema on both T2 and T1 with or without periosteal oedema on T1 and T2. From Gaeta <ul style="list-style-type: none"> a. loss of cortical signal void b. intracortical area of increased intensity c. subtle intracortical linear hyperintensity 	<ul style="list-style-type: none"> a. increased hypoattenuation (osteopenia*) b. intracortical hypoattenuation (resorption cavity) c. subtle intracortical linear hypoattenuation (striation)
IV	Fracture line present	Very large focal region of highly increased activity	Low signal fracture line on all sequences. Moderate to severe periosteal oedema on T1 and T2 Marrow oedema on both T1 and T2. May also show severe periosteal and moderate muscle oedema.	Hypoattenuating line

*Osteopenia = reduction of attenuation of 10% or more in cortical area